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(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : COE, Jotham, W. [US/US]; 151 Lamphere Road, Mystic, CT 06355 (US). FLIRI, Anton, F., J. [AT/US]; 596 West Thames Street, Norwich, CT 06360 (US). KANEKO, Takushi [JP/US]; 393 Northwood Drive, Guilford, CT 06437 (US). LARSON, Eric, R. [US/US]; 162 Lantern Hill Road, Mystic, CT 06355 (US).

(74) Agents: LUMB, J. Trevor et al.; Pfizer Inc., Patent Department, Eastern Point Road, Groton, CT 06340 (US).

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(54) Title: 2,4-DIAMINOQUINAZOLINES DERIVATIVES FOR ENHANCING ANTITUMOR ACTIVITY

(57) Abstract

2,4-diaminoquinazoline derivatives as potentiators of chemotherapeutic agents in the treatment of cancer.

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2,4-DIAMINOQUINAZOLINES DERIVATIVES FOR ENHANCING ANTITUMOR ACTIVITY

Background of the Invention

This invention relates to 2,4-diaminoquinazolines and their use as sensitizers of tumor cells to anti-cancer agents.

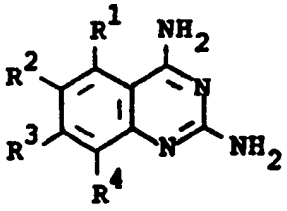
In cancer chemotherapy the effectiveness of anticancer drugs is often limited by the resistance of tumor cells. Some tumors such as of the colon, pancreas, kidney and liver are generally innately resistant, and other responding tumors often develop resistance during the course of chemotherapy. The phenomena of multidrug resistance (MDR) is characterized by the tumor cell's cross-resistance to structurally unrelated drugs. The drugs which are the target of resistance include adriamycin, daunomycin, vinblastine, vincristine, actinomycin D and etoposide. The resistance cells are often associated with over-expression of the mdr1 gene. This gene product is a family of 140-220 kd trans-membrane phosphoglycoprotein (P-glycoprotein) which functions as an ATP-dependent efflux pump. Thus, it has been postulated that this efflux mechanism keeps the intracellular level of the anticancer drug low, allowing the tumor cells to survive.

In recent years various substances such as verapamil, nifedipine and diltiazem have been used in in vitro experimental systems to reverse the MDR phenomena. More recently some of these agents have been tested clinically as MDR reversing agents. Little

efficacy has been observed with verapamil or trifluoroperazine. Thus, there is a need for an effective MDR reversing agent.

The 2,4-diaminoquinazolines are prepared by known methods utilizing 2,4-dichloroquinazolines [Postovskii and Goncharova, Zh. Obshch. Khim., 32, 3323 (1962)]. Curd et al. (J. Chem. Soc., 1947, 775) reported the synthesis of 2,4-dichloroquinazolines from the corresponding 2,4(1H, 3H)quinazolinedione. The Wellcome Foundation discloses 2,4-diaminoquinazolines of general structure D as antibacterials [GB patent 806772 (1958)]. Hess [US 3,511,836 (1970)] patented compounds of structures E, F, and G as antihypertensive agents. Wijbe [GB patent 1,390,014 (1975)] patented a process for compounds of structure H and these compounds are claimed to be antibacterials. Lacefield [US patent 3,956,495 (1976)] describes compounds of the general formula I as antithrombotic agents. Crenshaw [US patent 4,098,788 (1978)] patented a process for the production of compounds of formula J. Hess [European Patent 0,028,473 (1981)] describes chloro- and alkoxy-substituted 2,4-diaminoquinazolines of formula K. Ife et al. describe compounds of general structure L as inhibitors of gastric acid secretion [WO 89/0527 (1989)]. Compounds of structures M and N were published as phosphodiesterase inhibitors [Miller, J. Med. Chem., 28, 12 (1985)]. Richter et al. published compounds of structure O as inhibitors of dihydrofolate reductase [J. Med. Chem., 17, 943 (1974)]. In search

of compounds with herbicidal activity Miki et al. reported the synthesis of 2,4-dialkylaminoquinazolines (P) (Chem. Pharm. Bull. 30, 2313 (1982)]. Arylazidoprazosin (Q) has been shown to bind to P-glycoprotein [Safa et al., Biochem. Biophys. Res. Comm. 166, 259 (1990)].



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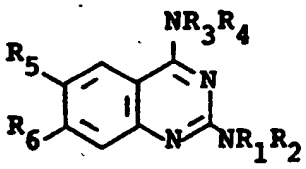

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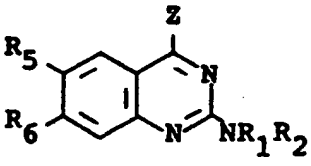

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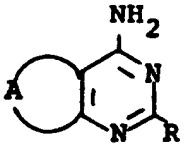

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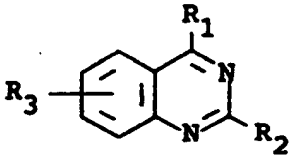

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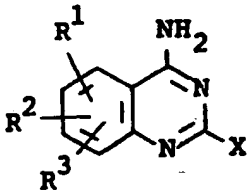

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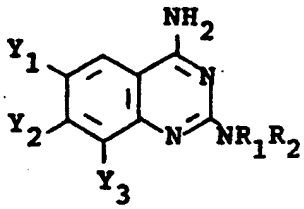

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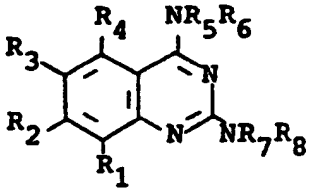

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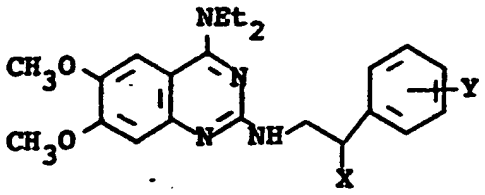

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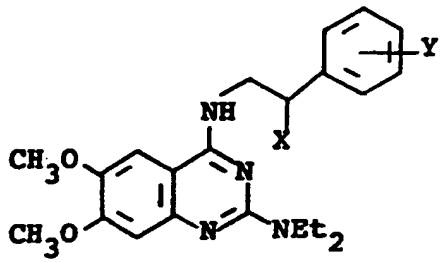

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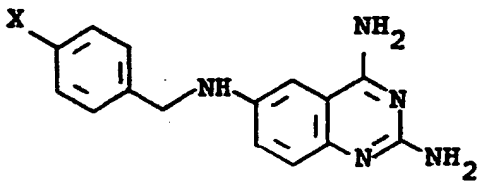

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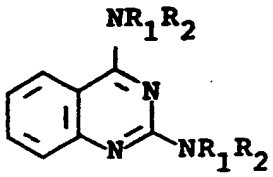

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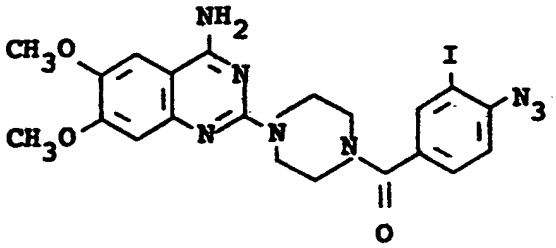

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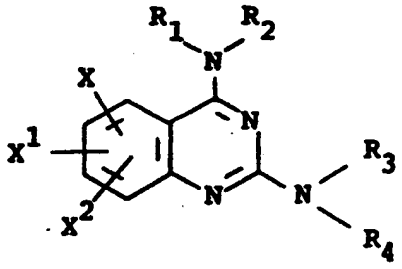
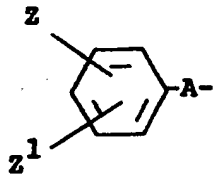
Summary of the Invention

The compound of the present invention are of the formula

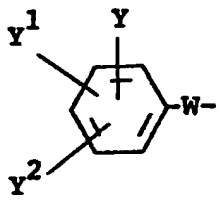


I

or a pharmaceutically acceptable acid addition salt thereof wherein X is alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, chloro, fluoro, amino, alkylamino of one to three carbon atoms, dialkylamino of two to six carbon atoms or trifluoromethyl; X^1 is hydrogen, alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, fluoro, chloro, dialkylamino of two to six carbon atoms; X^2 is hydrogen, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms; X and X^1 when taken together are ethylenedioxy or methylenedioxy; R_1 is hydrogen or alkyl of one to three carbon atoms; R_2 is alkyl of one to ten carbon atoms or aralkyl of the formula

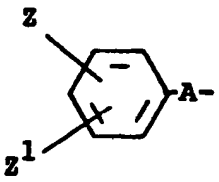


where Z and Z^1 are each hydrogen, alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino of two to six carbon atoms, A is a chemical bond or alkylene of one to four carbon atoms and Z and Z^1 when taken together are ethylenedioxy or methylenedioxy; R_3 is hydrogen or alkyl of one to three carbon atoms; R_4 is aralkyl of the formula

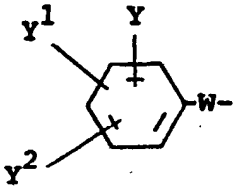


where W is alkylene of one to four carbon atoms, Y and Y^1 are each hydrogen, alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino of two to six carbon atoms, Y^2 is hydrogen, alkyl of one to three carbon atoms or alkoxy of one to three carbon atoms and Y^1 and Y^2 when taken together are ethylenedioxy or methylenedioxy; and R_3 and R_4 when taken together with the nitrogen to which they are attached are 4-phenylpiperazino, 4-alkoxyethoxypiperidino said alkoxy having from one to three carbon atoms or 4-alkoxycarbonylpiperazino said alkoxy having from one to three carbon atoms with the proviso that when X^1 and X^2 are each hydrogen, X is amino, alkylamino of one to three carbon atoms, dialkylamino of two to six carbon atoms or trifluoromethyl.

A preferred group of compounds are those wherein X and X^1 are each methoxy, R_1 is methyl, R_2 is aralkyl of the formula

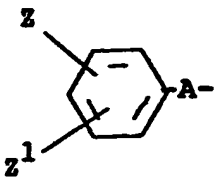


where Z is hydrogen, R_3 is hydrogen and R_4 is aralkyl of the formula

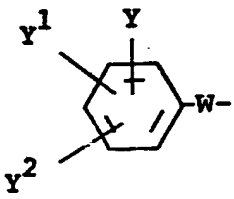


where W is $-(CH_2)_2-$, Y and Y^1 are each methoxy and Y^2 is hydrogen. Especially preferred within this group are the compounds where X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is 2-methoxy, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy, where X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy, where X is 6-methoxy, X^1 is 7-methoxy, X^2 is 8-methoxy, Z^1 is hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy, where X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is 4-fluoro, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

A second group of preferred compounds are those where X^2 is hydrogen, R_1 is methyl, R_2 is aralkyl of the formula



R^3 is hydrogen and R_4 is aralkyl of the formula



where W is $-(CH_2)_2-$, Y and Y^1 are each methoxy and Y^2 is hydrogen. Especially preferred within this group are the compounds where X is 6-methoxy, X^1 is 7-methoxy, Z is 3-methoxy, Z^1 is 4-methoxy, A is a chemical bond, Y is 2-methoxy and Y^1 is 3-methoxy, where X and X^1 are methylenedioxy, Z and Z^1 are each hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy and where X is 6-methoxy, X^1 is 7-methoxy, Z is 2-methoxy, Z^1 is 3-methoxy, A is $-CH_2$, Y is 3-methoxy and Y^1 is 4-methoxy.

The present invention also includes a method of inhibiting a P-glycoprotein in a mammal in need of such

treatment which comprises administering to said mammal a P-glycoprotein inhibiting amount of a compound of formula I. Preferred is the method where the mammal is a human suffering from cancer and said compound is administered with an anticancer effective amount of a chemotherapeutic agent.

Also included is a pharmaceutical composition for administration to a mammal which comprises a P-glycoprotein inhibiting amount of a compound of formula I, a pharmaceutically acceptable carrier and, optionally, an anticancer effective amount of a chemotherapeutic agent.

As previously indicated, the compounds of formula I form pharmaceutically acceptable acid addition salts. Said pharmaceutically acceptable acid addition salts include, but are not limited to, those with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid. In the case of those compounds of the formula (I) which contain a further basic nitrogen, it will, of course, be possible to form diacid addition salts (e.g., the dihydrochloride) as well as the usual monoacid addition salt.

As one skilled in the art recognized, compounds of formula I have the potential for containing asymmetric carbon atoms. All these potential isomers are considered within the scope of the present invention.

Detailed Description of the Invention

Compounds of the present invention are prepared with the reaction of a 2,4-dichloroquinazoline with an equivalent of an appropriate amine, R_1R_2NH, followed by the reaction of the product, a 2-chloro-4-aminoquinazoline derivative, with a second equivalent of an appropriate amine, R_3R_4NH.

In a more detailed description of the procedure, one molar equivalent of an optionally substituted 2,4-dichloroquinazoline and one molar equivalent of a tertiary amine-acid scavenger, such as triethylamine, N-methylmorpholine or diethylisopropylamine and one molar equivalent of an amine, R_1R_2NH, are combined in an anhydrous solvent such as dimethylacetamide, dioxane, chloroform, or N-methyl-2-pyrrolidone and maintained at from 0°C to about 25°C for a period of 1 to 48 hours.

The reaction mixture can be filtered and the filtrate concentrated to dryness <u>in vacuo</u>, or the reaction mixture can be quenched in water and the intermediate product either filtered or extracted with a water immiscible solvent such as methylene chloride or ethyl acetate. Removal of the extracting solvent provides the desired product. Frequently, the residue can be induced to crystallize by trituration with an organic solvent, and further purified by recrystallization or column chromatography.

The second step of the sequence leading to the products of the present invention consists of combining one molar equivalent of the appropriate 2-chloro-4-aminoquinazoline with either two molar equivalents of an amine, R_3R_4NH, or one equivalent of said amine and

one equivalent of a tertiary amine-acid scavenger as described above in a reaction-inert solvent such as ethoxyethoxyethanol, butanol, amyl alcohol or cyclohexanol for a period of 5 minutes to several hours at reaction temperatures of 100-200°C.

The reaction mixture can be cooled to room temperature and treated with a 1-N solution of an appropriate acid, such as hydrochloric acid to give a precipitate of the desired product as the hydrochloride salt. Other acids would give the corresponding acid addition salt. In instances where the acid addition salt does not precipitate the free base product can be isolated by chromatography of the crude material on silica gel using an eluant such as chloroform, ethyl acetate, diethyl ether, methanol methylene chloride, ethanol or mixtures thereof and subsequently converted to the acid addition salt product. The products are isolated by removing the eluting solvents in vacuo. Purification of the product can be done by recrystallization.

Generation of the free base from an acid addition salt can readily be carried out by treating an aqueous solution or suspension of the salt with at least one equivalent of an organic or inorganic base followed by extraction of the free base product with a water immiscible solvent such as ethyl acetate or methylene chloride. Removal of the solvent gives the desired base.

Compounds of formula I are inhibitors of the functions of P-glycoprotein, particularly human mdr 1 protein or P-glycoprotein related and membrane associate proteins which are participating in the

transport of xenobiotics or proteins across membranes e.g., cell membranes of eukariotic and proeukariotic origin e.g., pmfdr, however not exclusive or restricted to these examples.

Compounds enclosed in general formula I are useful in combination chemotherapy of cancer, malaria, viral infections such as AIDS, in therapy of septic shock syndrome or inflammation and may be useful in enhancing the tissue penetration of drugs where the penetration of these xenobiotics is limited due to the presence of P-glycoprotein or P-glycoprotein related functional proteins. Compounds of formula I increase the activity/efficacy of adriamycin, daunomycin, etoposide, epipodophyllotoxin congoners, actinomycin D, emetin, vincristin, vinblastin, chloroquine, antracycline antibiotics and of drugs which are structurally and functionally related to the above mentioned examples, in particular when the activity of these drugs has been shown to be limited due to the presence and function of P-glycoprotein, e.g. human mdr 1 protein or P-glycoprotein related proteins.

The compounds of the present invention are evaluated as potentiators of chemotherapeutic agents using a Cellular Drug Retention Assay. This assay was designed to study the effect of compounds on cellular retention of radiolabeled drug. In this case 14C-adriamycin retention by multidrug resistant human carcinoma cells, KBV1, is measured.

KBV1 cells are routinely grown in tissue culture as monolayers in DMEM high glucose medium containing

1 ug/ml vinblastine 10% heat inactivated fetal calf serum and supplemented with Glutamine, Pen-Strep and Garamycin.

The assay protocol (described below) should be applicable, with minor modifications, to a wide variety of cell lines grown in tissue culture.

Assay Protocol:

(1) Seed replicate 6-well tissue culture plates with 1.2 x 10E6 cells per 2 ml per well in absence of Vinblastine;

(2) Incubate 24 hrs at 37 degrees in humidified incubator (5% CO2);

(3) Aspirate off the spent media and overlay monolayers with 2 ml/well of fresh medium that is 2 uM in Adriamycin (2 uM unlabeled Adriamycin + 20000 cpm of 14C-Adr) and the test agent at concentrations varying from 0 to 100 uM;

(4) Following incubation for 3 hours at 37 degrees in humidified incubator, remove media and wash monolayers twice with 2 ml of ice-cold buffered saline;

(5) Detach monolayers using 0.5 ml of trypsin/EDTA, collect detached cells and transfer to scintillation vial. Rinse wells once with 0.5 ml of buffered saline and add to same vial containing cells;

(6) Add 5 ml of Beckman Ready-Safe scintillation fluid to vial, vortex and determine radioactivity per sample using a scintillation counter (10 minutes per sample);

(7) For background control: pre-incubate monolayers at 4 degrees for 15 minutes then remove media and add fresh ice-cold media containing Adr (see step

3). Following incubation for 3 hours at 4 degrees remove media and wash monolayers twice with 2 ml ice-cold buffered saline, then proceed as in step 5;

(8) Results are expressed as T/C and ED3x values as defined below:

T/C = pmoles Adr per 10E6 cells treated with test agent/
pmoles Adr per 10E6 untreated cells

ED3x = concentration of test agent that produces a 3 fold increase in cellular accumulation of radiolabeled Adr, i.e. T/C = 3.

Calculations:

Specific cpm = [sample cpm - background cpm]
Specific activity = [cpm/total conc. of Adr]
pmoles Adr = [specific cpm/specific activity]
pmoles Adr per 10E6 cells = [(pmoles Adr per well/number of cells per well) x 10E6 cells]

As previously mentioned compounds of the present invention and salts thereof are useful in potentiating the anticancer effects of chemotherapeutic agents. Such agents can include adriamycin, daunomycin, aclacinomycin A, actinomycin C, actinomycin D, mithramycin, toyomycin, vinblastine, maytansine, bruceantin, homoharintonin, anguindin, neocarcinostatin, mitomycin C and anthramycin.

The compounds of the present invention can be administered with, 24 hours before or up to 72 hours after the administration of the chemotherapeutic agents. When administered with said agents, they can

be taken either separately or coadministered in the same formulation.

The compounds of the present invention whether taken separately or in combination with an anti-cancer agent, are generally administered in the form of pharmaceutical compositions comprising at least one of the compounds of formula I and optionally a chemotherapeutic agent, together with a pharmaceutically acceptable vehicle or diluent. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration: for oral administration, in the form of tablets, hard or soft gelatin capsules, suspensions, granules, powders and the like, and, for parenteral administration, in the form of injectable solutions or suspensions, and the like.

For use in the potentiation of anti-cancer agents in a mammal, including man, a compound of formula I is given in an amount of about 0.5-100 mg/kg/day, in single or divided doses. A more preferred dosage range is 2-50 mg/kg/day, although in particular cases, at the discretion of the attending physician, doses outside the broader range may be required. The preferred route of administration is generally oral, but parenteral administration (e.g. intramuscular, intravenous, intradermal) will be preferred in special cases, e.g., where oral absorption is impaired as by disease, or where the patient is unable to swallow.

The present invention is illustrated by the following examples, but is not limited to the details or scope thereof.

EXAMPLE 1

2-(3,4-Dimethoxyphenethylamino)-4-(N-methyl-benzyl-amino)-6,7-dimethoxyquinazoline hydrochloride ($X = 6\text{-}CH_3O$; $X^1 = 7\text{-}CH_3O$; $X^2 = H$; $R_1 = CH_3$; $R_2 = C_6H_5CH_2\text{-}$; $R_3 = H$; and $R_4 = 3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2\text{-}$)

A. 2-chloro-4-(N-methyl-benzylamino)-6,7-dimethyl-quinazoline

To a solution of 26 g of 2,4-dichloro-6,7-dimethoxyquinazoline and 10 g of triethylamine in 350 ml of dry dimethylacetamide was added 12 g of N-methyl-benzylamine. The reaction mixture was stirred at room temperature for 5 hrs and was then diluted with 1000 ml of water. The precipitated product was filtered, washed with water (1 x 200 ml) and suspended in 200 ml of hot ethanol. A sample was recrystallized from methanol, m.p. 187-188°C.

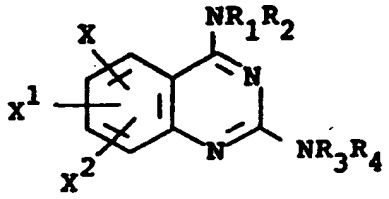
B. 2-(3,4-dimethoxyphenethylamino)-4-(N-methyl-benzylamino)-6,7-dimethoxyquinazoline hydro-chloride

A mixture of 1.03 g of the product from Example 1A, 543 mg of 3,4-dimethoxyphenethylamine and 387 mg of diisopropylethylamine in 2 g of ethoxyethoxyethanol was heated with stirring for 2 hrs under a nitrogen atmosphere. The reaction mixture was cooled, diluted with a small amount of chloroform and applied to a column of silica gel (30 g). The column was eluted with chloroform and then 2% methanol in chloroform (V:V). The fractions containing the product were combined and concentrated in vacuo to a yellow-residue. The residue was dissolved in 1N hydrochloric acid in

methanol and the resulting precipitate filtered and dried, 550 mg, m.p. 201-202°C, M^+ = 489.2.

EXAMPLES 2-37

Employing the procedure of Example 1A and B and starting with the appropriate reagents, the following compounds were prepared:



Example 2: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 2-$CH_3OC_6H_4CH_2$-; R_3 = H and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 204.5-206°C, M^+ = 519.2.

Example 3: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = 3,4-$(CH_3O)_2C_6H_3$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 231-233°C, M^+ 521.0.

Example 4: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = 3,4-$(CH_3O)_2C_6H_3$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 236-238°C, M^+ = 521.0.

Example 5: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 3,4-$(CH_3O)_2C_6H_3$-; R_3 = H; and R_4 = 3,4$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 250°C, M^+ 475.2.

Example 6: X, X^1 and X^2 = H; R_1 = H; R_2 = C_6H_5-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 231.5-232.5°C, M^+ 401.0.

Example 7: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 3,4-$(CH_3O)_2C_6H_3$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 212-213°C, M^+ 475.2.

Example 8: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = C_6H_5-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 109-112°C (free base), M^+ 460.5.

Example 9: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 3-Cl-4-F$C_6H_3CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 129-131°C, M^+ 541.2.

Example 10: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 2,6-$(CH_3O)_2C_6H_3CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 177-179°C, M^+ 549.3.

Example 11: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = $C_6H_5CH_2$; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 249-251°C, M^+ 474.5.

Example 12: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 245-248°C, M^+ 475.1.

Example 13: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 210-211°C, M^+ 488.3.

Example 14: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2-$ClC_6H_4(CH_2)_2$-; m.p. 218-219°C, M^+ 462.2.

Example 15: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 83-86°C, M^+ 563.4.

Example 16: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3-$CH_3OC_6H_4(CH_2)_2$-; m.p. 194-195°C, M^+ 459.3.

Example 17: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2-Br-3,4-$(CH_3O)_2$-$C_6H_2(CH_2)_2$-; m.p. 219-220°C, M^+ 569.0.

Example 18: X + X^1 = 6,7-O_2CH_2; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 205-207°C (free base), M^+ 473.0.

Example 19: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = C_2H_5; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 171.5-172.5°C, M^+ 503.3.

Example 20: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = C_2H_5; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 4-$C_2H_5OC_6H_4$-$(CH_2)_2$-; m.p. 192-194.5°C, M^+ 473.5.

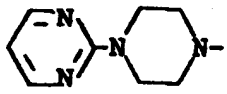
Example 21: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = 8-CH_3O; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 199-201°C, M^+ 519.2.

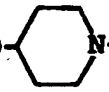
Example 22: X, X^1 and X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 95-98°C (free base), M^+ 429.1.

Example 23: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = C_2H_5; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 4-ClC_6H_4-$(CH_2)_2$-; m.p. 210-212°C, M^+ 463.2.

Example 24: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 4-$FC_6H_4CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3$-$(CH_2)_2$-; m.p. 185-187°C, M^+ 507.0.

Example 25: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = 3,4-$(CH_3O)_2C_6H_3CH_2$-; R_3 = H; and R_4 = $C_6H_5CH_2$-; m.p. 144-145°C (free base), M^+ 497.0.

Example 26: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = $C_6H_5CH_2$-; and R_3R_4N =  ; m.p. 278-281°C, M^+ 458.0.

Example 27: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = $C_6H_5CH_2$-; and R_3R_4N- = $C_2H_5O(CH_2)_2O$-  -; m.p. 213-215°C, M^+ 467.0.

Example 28: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = $C_6H_5CH_2$-; m.p. 196-199°C, M^+ 542.0.

Example 29: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = 3,4-$(CH_3O)_2C_6H_3$-; and R_3, R_4 = C_2H_5; M^+ 493.4 (free base).

Example 30: X = 6-C_2H_5O; X^1 = 7-C_2H_5O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 187-188°C, M^+ 517.5.

Example 31: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = CH_3; and R_4 = 3,4-$(CH_3O)_2C_6H_3$-$(CH_2)_2$-; m.p. 183-185°C, M^+ 503.3.

Example 32: X and X^1 = H; X^2 = 8-CH_3O; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 162-164°C (free base), M^+ 459.0.

Example 33: X and X^1 = H; X^2 = 8-CH_3O; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2-$ClC_6H_4(CH_2)_2$-; m.p. 185-186°C (free base), M^+ 433.0.

Example 34: X and X^1 = H; X^2 = 8-CH_3O; R_1 = CH_3; R_2 = $C_6H_5CH_2$-; R_3 = H; and R_4 = 2,3-$(CH_3O)_2C_6H_3(CH_2)_2$-; m.p. 182-184.5°C (free base), M^+ 459.0.

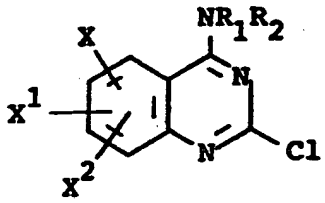
Example 35: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = H; R_2 = C_6H_5-; and R_3R_4N = C_2H_5OCON  -; M^+ 438.0.

Example 36: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = $CH_3(CH_2)_3$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2C_6H_3$-$(CH_2)_2$-; m.p. 160-162°C, M^+ 455.2.

Example 37: X = 6-CH_3O; X^1 = 7-CH_3O; X^2 = H; R_1 = CH_3; R_2 = 2,3-$(CH_3O)_2C_6H_3CH_2$-; R_3 = H; and R_4 = 3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$-; m.p. 103-105°C, M^+ 549.2.

PREPARATION A

Starting with the requisite reagents and employing the procedure of Example 1A, the following intermediates were prepared:

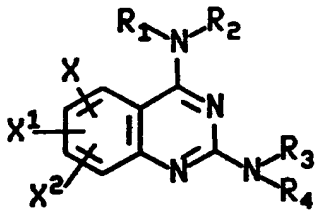


X	X^1	X^2	R_1R_2N	m.p., °C
6-CH_3O	7-CH_3O	H	2-$CH_3OC_6H_4CH_2\overset{|}{N}CH_3$	168-171.5
6-CH_3O	7-CH_3O	H	3,4-$(CH_3O)_2C_6H_3NH$-	250-251
H	H	H	C_6H_5NH-	189-191
6-CH_3O	7-CH_3O	H	3,4-$(CH_3O)_2C_6H_3\overset{|}{N}CH_3$	216-218
6-CH_3O	7-CH_3O	H	C_6H_5NH-	220-222
6-CH_3O	7-CH_3O	H	3-Cl-4-$FC_6H_3CH_2\overset{|}{N}CH_3$	152-154
6-CH_3O	7-CH_3O	H	2,6-$(CH_3O)_2C_6H_3CH_2\overset{|}{N}CH_3$	155-158
6-CH_3O	7-CH_3O	H	$C_6H_5CH_2NH$-	209-210
6-CH_3O	7-CH_3O	H	$C_6H_5CH_2\overset{|}{N}CH_3$-	187-188
6-CH_3O	7-CH_3O	H	3,4-$(CH_3O)_2C_6H_3(CH_2)_2\overset{|}{N}CH_3$	132-136

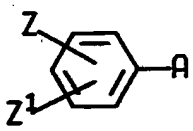
X	X^1	X^2	R_1R_2N	m.p., °C
6,7-OCH_2O-		H	$C_6H_5CH_2\overset{\vert}{N}CH_3$	155-157
6-CH_3O	7-CH_3O	H	$C_6H_5CH_2\overset{\vert}{N}C_2H_5$	128-130
6-CH_3O	7-CH_3O	8-CH_3O	$C_6H_5CH_2\overset{\vert}{N}CH_3$	122-123
H	H	H	$C_6H_5CH_2\overset{\vert}{N}CH_3$	98-99
6-CH_3O	7-CH_3O	H	4-$FC_6H_4CH_2\overset{\vert}{N}CH_3$	175-177
6-CH_3O	7-CH_3O	H	3,4-$(CH_3O)_2C_6H_3CH_2NH$-	
6-C_2H_5O	7-C_2H_5O	H	$C_6H_5CH_2\overset{\vert}{N}CH_3$	159-160
H	H	8-CH_3O	$C_6H_5CH_2\overset{\vert}{N}CH_3$	115-115.5
6-CH_3O	7-CH_3O	H	$CH_3(CH_2)_3\overset{\vert}{N}CH_3$	180-182
6-CH_3O	7-CH_3O	H	2,3-$(CH_3O)_2C_6H_3CH_2\overset{\vert}{N}CH_3$	

CLAIMS

1. A compound of the formula

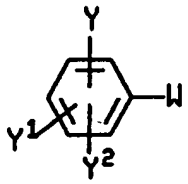


or a pharmaceutically acceptable acid addition salt thereof, wherein X is alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, chloro, fluoro, amino, alkylamino having one to three carbon atoms, dialkylamino having two to six carbon atoms or trifluoromethyl; X^1 is hydrogen, alkyl having one to three carbon atoms, fluoro, chloro or dialkylamino having two to six carbon atoms; X_2 is hydrogen, alkyl having one to three carbon atoms or alkoxy having one to three carbon atoms; X and X^1 when taken together are ethylenedioxy or methylenedioxy; R_1 is hydrogen or alkyl having one to three carbon atoms; R_2 is alkyl having one to ten carbon atoms or aralkyl of the formula



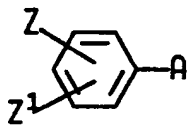
where Z and Z^1 are each hydrogen, alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino having two to six carbon atoms, A is a chemical bond or alkylene having from one to four carbon atoms and Z and Z^1 when taken together are ethylenedioxy or

methylenedioxy; R_3 is hydrogen or alkyl having one to three carbon atoms; R_4 is aralkyl of the formula

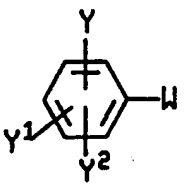


where W is alkylene having one to four carbon atoms, Y and Y^1 are each hydrogen, alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino having two to six carbon atoms, Y^2 is hydrogen, alkyl having one to three carbon atoms or alkoxy having one to three carbon atoms and Y^1 and Y^2 when taken together are ethylenedioxy or methylenedioxy; and R_3 and R_4 when taken together with the nitrogen to which they are attached are 4-phenylpiperazino, 4-alkoxyethoxypiperidino said alkoxy having from one to three carbon atoms or 4-alkoxycarbonylpiperizino said alkoxy having one to three carbon atoms, with the proviso that when X^1 and X^2 are each hydrogen X is amino, alkylamino having one to three carbon atoms, dialkylamino having two to six carbon atoms or trifluoromethyl.

2. A compound of claim 1, wherein X and X^1 are each methoxy, R_1 is methyl, R_2 is aralkyl of the formula



where Z is hydrogen, R_3 is hydrogen and R_4 is aralkyl of the formula



where W is $-(CH_2)_2-$, Y and Y^1 are each methoxy and Y^2 is hydrogen.

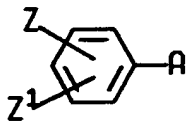
3. The compound of claim 2, wherein X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is 2-methoxy, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

4. The compound of claim 2, wherein X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

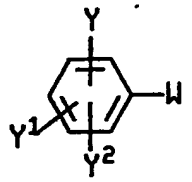
5. The compound of claim 2, wherein X is 6-methoxy, X^1 is 7-methoxy, X^2 is 8-methoxy, Z^1 is hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

6. The compound of claim 2, wherein X is 6-methoxy, X^1 is 7-methoxy, X^2 is hydrogen, Z^1 is 4-fluoro, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

7. A compound of claim 1, wherein X^2 is hydrogen, R_1 is methyl, R_2 is aralkyl of the formula



R_3 is hydrogen and R_4 is aralkyl of the formula



where W is $-(CH_2)_2-$, Y and Y^1 are each methoxy and Y^2 is hydrogen.

8. The compound of claim 7, wherein X is 6-methoxy, X^1 is 7-methoxy, Z is 3-methoxy, Z^1 is 4-methoxy, A is a chemical bond, Y is 2-methoxy and Y^1 is 3-methoxy.

9. The compound of claim 7, wherein X and X^1 are 6,7-methylenedioxy, Z and Z^1 are each hydrogen, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

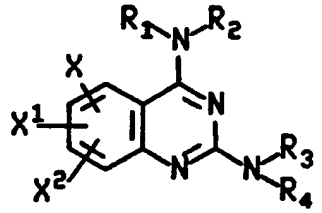
10. The compound of claim 7, wherein X is 6-methoxy, X^1 is 7-methoxy, Z is 2-methoxy, Z^1 is 3-methoxy, A is $-CH_2-$, Y is 3-methoxy and Y^1 is 4-methoxy.

11. A method of inhibiting a P-glycoprotein in a mammal in need of such treatment which comprises administering to said mammal a P-glycoprotein inhibiting amount of a compound according to claim 1.

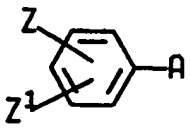
12. A method of claim 11, wherein the mammal is a human suffering from cancer and said compound is administered before, with or after the administration to said human of an anticancer effective amount of a chemotherapeutic agent.

13. A pharmaceutical composition for administration to a mammal which comprises a P-glycoprotein inhibiting amount of a compound of claim 1, a pharmaceutically acceptable carrier and, optionally, an anticancer effective amount of a chemotherapeutic agent.

14. A process for preparing a compound of the formula

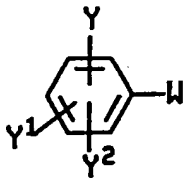


and a pharmaceutically acceptable acid addition salt thereof, wherein X is alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, chloro, fluoro, amino, alkylamino having one to three carbon atoms, dialkylamino having two to six carbon atoms or trifluoromethyl; X^1 is hydrogen, alkyl having one to three carbon atoms, fluoro, chloro or dialkylamino having two to six carbon atoms; X_2 is hydrogen, alkyl having one to three carbon atoms or alkoxy having one to three carbon atoms; X and X^1 when taken together are ethylenedioxy or methylenedioxy; R_1 is hydrogen or alkyl having one to three carbon atoms; R_2 is alkyl having one to ten carbon atoms or aralkyl of the formula

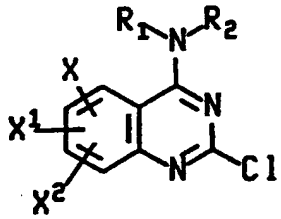


where Z and Z^1 are each hydrogen, alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino having two to six carbon atoms, A is a chemical bond or alkylene having from one to four carbon atoms and Z and Z^1 when taken together are ethylenedioxy or

methylenedioxy; R_3 is hydrogen or alkyl having one to three carbon atoms; R_4 is aralkyl of the formula



where W is alkylene having one to four carbon atoms, Y and Y^1 are each hydrogen, alkyl having one to three carbon atoms, alkoxy having one to three carbon atoms, fluoro, chloro, bromo, trifluoromethyl or dialkylamino having two to six carbon atoms, Y^2 is hydrogen, alkyl having one to three carbon atoms or alkoxy having one to three carbon atoms and Y^1 and Y^2 when taken together are ethylenedioxy or methylenedioxy; and R_3 and R_4 when taken together with the nitrogen to which they are attached are 4-phenylpiperazino, 4-alkoxyethoxypiperidino said alkoxy having from one to three carbon atoms or 4-alkoxycarbonylpiperizino said alkoxy having one to three carbon atoms, with the proviso that when X^1 and X^2 are each hydrogen X is amino, alkylamino having one to three carbon atoms, dialkylamino having two to six carbon atoms or trifluoromethyl, which comprises reacting a compound of the formula



wherein R_1, R_2, X, X^1 and X^2 are defined with a compound of the formula

$$R_3R_4NH$$

where R_3 and R_4 are defined in a reaction-inert solvent containing one equivalent of an amine-acid scavenger at a reaction temperature of 100-200°C until the reaction is substantially complete.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/00028

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D239/95; C07D401/04; C07D401/14; C07D403/12
A61K31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category*	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 322 133 (SMITH KLINE) 28 June 1989 cited in the application see claims	1,2, 11-14
A	US,A,3 663 706 (H-J. HESS) 16 May 1972 see column 13 - column 18; claims; tables 2,4	1,2, 11-14
X	JOURNAL OF MEDICINAL CHEMISTRY. vol. 28, no. 1, 1985, WASHINGTON US pages 12 - 17; J. MILLEN ET AL.: '2-(BETA-ARYLETHYLAMINO)- AND 4-(beta-ARYLETHYLAMINO)QUINAZOLINES as PHOSPHODIESTERASE INHIBITORS' cited in the application see page 16 - page 17	1,2, 11-14

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 MARCH 1992	31.03.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FRANCOIS J.C.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9200028 SA 55905

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/03/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0322133	28-06-89	AU-A-	2823089	05-07-89
		CN-A-	1033380	14-06-89
		WO-A-	8905297	15-06-89
		JP-T-	2502462	09-08-90
US-A-3663706	16-05-72	US-A-	3635979	18-01-72